



PCT/GB 00/03729

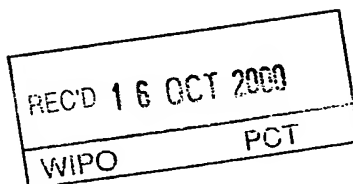
GB00/3729



INVESTOR IN PEOPLE

4

The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ



I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.

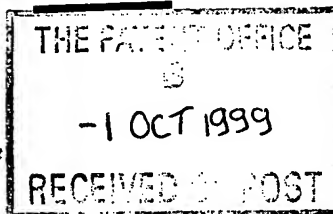


Signed *Andrew Gervy*
Dated 5 October 2000

**PRIORITY
DOCUMENT**

SUBMITTED OR TRANSMITTED IN
COMPLIANCE WITH RULE 17.1(a) OR (b)

The
Patent
Office



01OCT99 E480731-1 000244
P01/7700 0.00 - 9923139.1

The Patent Office

Cardiff Road
Newport
Gwent NP9 1RH

Request for grant of a patent
(See the notes on the back of this form. You can also get
an explanatory leaflet from the Patent Office to help
you fill in this form)

1. Your reference

RFB/P60262GB

2. Patent application number
(The Patent Office will fill in this part)

9923139.1

1 OCT 1999

3. Full name, address and postcode of the or of
each applicant (underline all surnames)

NORTON HEALTHCARE LTD
ALBERT BASIN
ROYAL DOCKS
LONDON
E16 2QT
W188221003

Patents ADP number (if you know it)

If the applicant is a corporate body, give the
country/state of its incorporation

4. Title of the invention

ANTI-INFLAMMATORY PHARMACEUTICAL
FORMULATIONS

5. Name of your agent (if you have one)

WIRQUHART - DYKES & LORD

"Address for service" in the United Kingdom
to which all correspondence should be sent
(including the postcode)

TOWER HOUSE
MERRION WAY
LEADS
LS2 8PA

Patents ADP number (if you know it)

1644004

6. If you are declaring priority from one or more
earlier patent applications, give the country
and the date of filing of the or of each of these
earlier applications and (if you know it) the or
each application number

Country

Priority application number
(if you know it)

Date of filing
(day / month / year)

7. If this application is divided or otherwise
derived from an earlier UK application,
give the number and the filing date of
the earlier application

Number of earlier application

Date of filing
(day / month / year)

8. Is a statement of inventorship and of right
to grant of a patent required in support of
this request? (Answer 'Yes' if:

- a) any applicant named in part 3 is not an inventor, or
 - b) there is an inventor who is not named as an
applicant, or
 - c) any named applicant is a corporate body.
- See note (d))

YES

ANTI-INFLAMMATORY PHARMACEUTICAL FORMULATIONS

This invention relates to pharmaceutical formulations of anti-inflammatory drugs, particularly non-steroidal anti-inflammatory drugs (NSAIDs).

These NSAIDs are used for the treatment of inflammatory conditions such as osteoarthritis or rheumatoid arthritis. A side effect of the oral administration of NSAIDs particularly with long term usage, is a liability to ulcerogenic effects. NSAID induced ulcers in the stomach are potentially dangerous because few or no symptoms may be detected until significant damage has been caused. Certain prostaglandins, for example misoprostol have been shown to reduce and even prevent such ulcers.

Various patent applications relate to use of misoprostol with immediate release drugs, for example GB-A-2135881 (Farmitalia Carlo Erba), WO91/16896 (G D Searle), or where a gastric resistant coating is put over the NSAID in an attempt to reduce further gastric erosion due to release in the stomach of the NSAID, for example WO91/16895, WO91/16886 (G D Searle).

There is an increasing use of sustained release preparations of NSAID drugs to reduce the number of doses required by the patient each day. Although the theory of such preparations is that the majority of the drug is released in the intestine rather than the stomach, in practice there is a significant occurrence of gastric problems. This may be due to release of small amounts of drug within the stomach.

The incorporation of misoprostol into such products to reduce the potential for such problems has not previously been disclosed.

According to the present invention an oral pharmaceutical dosage form includes a mixture of a delay release formulation of a NSAID and a mixture containing one or more excipients and a prostaglandin.

The delay release NSAID formulation preferably comprises coated beads or pellets.

An alternative formulation comprises coated granules.

The prostaglandin mixture may be provided in the form of a powder which is mixed with the NSAID formulation within the dosage form.

The dosage form may comprise a tablet, capsule, granule or other commonly used configuration. However preferred dosage forms comprise a capsule containing multi-particulate beads or granules of the NSAID formulation together with the powdered prostaglandin mixture. The NSAID beads or granules preferably have coatings adapted to provide programmed release according to the position in the gastrointestinal tract. Use of such coated beads or granules provides a more repeatable release along the gastrointestinal tract and may reduce gastric erosion because the small pellets or beads are easily moved and do not adhere readily to the folds of the gastric wall.

Beads or granules for use in accordance with this invention may have a single slowly erodible coat or may comprise mixtures of beads or granules with differing levels or types of coating adapted to provide a continuous or distributed release profile through the gastrointestinal tract. The delay afforded may range from a minimal delay to several hours, dependent on the pH of the gastrointestinal tract in the immediate vicinity.

The NSAID is preferably but not exclusively one of reasonably low weight per standard dose, that is 200 mg or below. Examples of suitable NSAIDs include tiaprofenic acid, piroxicam, flubiprofen, tenoxicam, meloxicam or similar molecules. Salts or other derivatives of these drugs may be employed in a conventional manner. Most preferably the drug is diclofenac sodium, ketoprofen or indomethacin. Mixtures may be used.

It is possible to produce the pellets or beads by conventional means. Techniques that can be used can include coating the drug on a non-pariel core preferably composed of inert sugar or similar substance and then overcoating with the required coating before encapsulation. The following steps may be employed.

- i. Preparation of inert core by conventional pan coating method
- ii Active coating by using rotary type fluidized bed.
- iii Protective coating by using rotary type fluidized bed.
- iv Enteric coating by using rotary type fluidized bed.

The procedure disclosed in EP-A-519144 may be used.

Drug delivery using capsules avoids a further compression step as may be necessary during tablet manufacture.

An alternative method is to form beads or pellets by co-acervation or alternatively by precipitation from solution as described by Zaniboni, Fell and Collett, (Int.J.Pharm, 1995, 125, 151-5).

In a preferred technique the beads may be formed by spheronisation, roto granulation or a similar technique. If tablets are to be made, preferably the beads should be soft enough to deform slightly under compression to avoid cracking but not too soft so as to deform significantly as deformation may also cause cracking or rupture of the coat. A mixture of drug with a suitable amount of an excipient or excipients can be found by simple experiments. Suitable excipients include polyvinyl pyrrolidone, sugars and cellulose derivatives particularly microcrystalline cellulose.

Granules, for example composed of diclofenac sodium and a methyl methacrylate (eg Eudragit L 30 D-55) may be prepared by blending the ingredients in a planetary mixer with slow addition of water to produce granules. In a preferred process very fine granules are produced to avoid a need for milling before compaction into tablets or incorporation into capsules. Layered tablets may be produced by coating these granules.

An alternative method of forming coated granules is by spraying a solution of Eudragit onto a bed of diclofenac sodium in a fluid bed coating apparatus. The process is preferably controlled to produce fine granules which do not require milling before incorporation into tablets or capsules.

The coating for the beads may include cellulose derivatives eg hydroxypropyl methyl cellulose, methacrylic acid and derivatives eg methyl methacrylates for example, Eudragit® (Rhom Pharm), especially Eudragit L or S. Other standard enteric coating materials may be used for example phthalate, eg cellulose acetate phthalate or preferably hydroxypropylacetate phthalate or polyvinylacetate phthalate. Mixtures of these and other materials may be used to produce delay release coated beads. Normally the coating will include plasticisers eg polyethylene glycol, triacilin or phthalate esters.

The prostaglandin component preferably contains misoprostol optionally together with one or more inert excipients. The prostaglandin is normally provided as a 1:10 or 1:100 dilution on an inert cellulose or other binder or filler. Especially useful material for this invention is hydroxypropyl methyl cellulose. The dosage of prostaglandin may be chosen to be suitable to prevent or reduce stomach ulceration caused by the NSAID. A

suitable dose of misoprostol is between 10 - 50 μg preferably 50 - 200 μg per dosage form but this may be increased or decreased depending on the NSAID used.

Preferred dosage forms comprise capsules, preferably hard gelatin capsules.

In preferred embodiments of the invention, the potential for gastric erosion is reduced by ensuring that the prostaglandin is released before the NSAID. Any beads for immediate or rapid release are coated with an inert coating which defer solubility in gastric fluid, for example for a period of 30 minutes. Such materials include cellulose derivatives for example hydroxypropyl methyl cellulose, methyl or ethyl celluloses or other sealants eg Zein. Thin coatings of methacrylate derivatives eg polyhydroxymethacrylate or other materials such as hardened gelatine, waxes, starches or polyvinyl pyrrolidone may be used. Other portions of the beads may be coated with methacrylate derivatives, phthalate, for example hydroxypropyl methyl cellulose phthalate or similar materials to give an appropriate release profile as is well known in the art.

The invention is further described by means of example, but not in any limitative sense.

Example 1

Hard gelatin capsules fill was prepared containing a mixture of the following:

delay release ketoprofen beads	250 mg
misoprostol (diluted 1:100 on hydroxypropylmethylcellulose)	20 mg
lactose (anhydrous)	160 mg
hydrogenated vegetable oil	4 mg

The beads were prepared by spray coating a suspension or solution of ketoprofen onto a non-pareil sugarcore, together with a binder eg polyvinylpyrrolidone or hydroxypropylmethyl cellulose. The beads were subsequently coated with a delay release coating eg methylmethacrylate (eg Eudragit (Trade Mark)). Mixtures of beads with various levels of coating were used to give the required therapeutic release pattern.

In a fluidized bed apparatus, uniform spherical inert sugar sphere cores were coated with a first layer consisting of the compounds, an inert water soluble polymer such as hydroxy-propylmethylcellulose or hydroxypropylcellulose, and talc. The second layer consisted of an inert water soluble polymer such as hydroxypropylmethylcellulose or hydroxypropylcellulose, talc and a pigment such as titanium dioxide. The third and enteric coating layer consisted of an enteric coating polymer such as co-polymerized methacrylic acid/methacrylic acid methyl esters, a plasticiser such as triethyltrate or similar plasticisers, and talc.

The layers were applied by conventional fluidized bed coating techniques using aqueous solutions or dispersions.

Pseudo zero release was obtained by use of a mixture of beads released at various pHs or at various times dependent on the type of coating.

The beads in Example 1 contained 40% ketoprofen giving a dose per capsule of 100 mg plus 100 μ g misoprostol.

The mix was then filled into suitable hard gelatine capsules.

Example 2

The following formulation was employed:

delay release diclofenac beads	214 mg
microcrystalline cellulose (dried)	
eg Avicel R PH112	150 mg
misoprostol (1 in 100 dilution on HPMC)	20 mg
stearic acid	4 mg
talc	8 mg

Example 3

The following formulation was mixed with water in a planetary mixer to make enteric coated granules:

diclofenac sodium	96.2%
Eudragit L 30 D-55	3.8%

The granules were dried and compacted into layered tablets having the following composition:

diclofenac-containing granules	26.0%
microcrystalline cellulose	73.5%
magnesium stearate	0.5%

The tablets are compared to a proprietary diclofenac-containing tablet available under the trade mark Arthrotec. Bioequivalence studies showed the properties to be essentially similar.

Beads containing 35% diclofenac sodium ie 75 mg drug per dose were prepared.

The beads were formed as previously described, or by mixing with a bulking agent eg microcrystalline cellulose, moistening with water, extruding and spheronising to give spherical or ovoid particles about 0.5 mm to 1.5 mm in diameter. These were dried and coated as previously described using a standard coating agent. The beads were mixed as required to give the required release profile.

The beads are usually provided with a coating to prevent immediate release in the stomach, particularly release before the misoprostol has dissolved.

CLAIMS

1. An oral pharmaceutical dosage form including a mixture of a delay release formulation of a non-steroidal anti-inflammatory drug (NSAID) and a mixture containing a prostaglandin and one or more excipients.
2. A dosage form as claimed in claim 1, wherein the NSAID formulation comprises coated pellets, beads or granules.
3. A dosage form as claimed in claim 1, wherein the prostaglandin is misoprostol.
4. A dosage form as claimed in claim 1, wherein the prostaglandin mixture is a powder.
5. A dosage form as claimed in claim 2, comprising a capsule containing multi-particulate pellets, beads or granules of the NSAID formulation together with the powdered prostaglandin mixture.
6. A dosage form as claimed in claim 2, comprising a mixture of pellets, beads or granules with different levels or types of coating.
7. A dosage form as claimed in claim 1, wherein the NSAID is selected from the group consisting of tiaprofenic acid, piroxicam, flubiprofen, tenoxicam, meloxicam and salts and derivatives thereof.
8. A dosage form as claimed in claim 7, wherein the NSAID is selected from the group consisting of diclofenac sodium, ketoprofen and indomethacin and mixtures thereof.

9. A dosage form as claimed in claim 3, wherein the dosage of misoprostol is 50 to 200 μ g per dosage form.

10. A dosage form as claimed in claim 2, wherein the pellets or beads comprise coatings including the drug on non-pareil cores.

11. A dosage form as claimed in claim 2, wherein the pellets or beads are made by co-acervation or precipitation from solution.

12. A dosage form as claimed in claim 10, wherein the beads are made by spheronisation or roto granulation.

13. A dosage form as claimed in claim 10, wherein the coating includes the drug and an excipient selected from the group consisting of: polyvinyl pyrrolidone, sugars and cellulose derivatives.

14. A dosage form as claimed in claim 2, wherein the pellets, beads or granules have a coating of compounds selected from the group consisting of: hydroxypropyl methyl cellulose, methacrylic acid and derivatives, methyl methacrylates, cellulose acetate phthalate, hydroxypropylacetate phthalate, polyvinylacetate phthalate and mixtures thereof.

15. A dosage form as claimed in claim 14, wherein the coating includes a plasticiser selected from the group consisting of: polyethylene glycol, triacilin or phthalate esters.

16. A dosage form as claimed in claim 1 comprising a filled hard gelatin capsule.

ABSTRACT

An oral pharmaceutical dosage form including a mixture of a delay release formulation of a non-steroidal anti-inflammatory drug (NSAID) and a mixture containing a prostaglandin and one or more excipients.

